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Primary Sclerosing Cholangitis and the management of uncertainty and complexity

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Abstract

Primary Sclerosing cholangitis (PSC) is a rare chronic auto-immune disease with no effective therapy and a large unmet need for new treatments. Patients require significant healthcare resources over their lifetime with high rates of hospital admission, malignancy, liver transplantation and death. As a rare disease, expertise in management can be limited to large referral liver transplant programmes, and even then there is frequently variation in practice. In this case-based review, we aim to discuss common clinical dilemmas encountered by clinicians managing patients with PSC and address related competencies in the 2010 Gastroenterology Curriculum.

Introduction

Primary sclerosing cholangitis (PSC) is a rare auto-immune liver disorder with no effective therapeutic intervention yet an ongoing high morbidity, mortality and hepato-biliary/colonic cancer risk. Current management aims towards symptomatic treatment, facilitation of clinical trials and appropriate but timely referral for liver transplantation. Diagnosis and risk stratification for progressive disease is challenging, with an often unpredictable course complicated in most cases by co-morbid inflammatory bowel disease. This clinical review will address the related competencies described in the 2010 Gastroenterology Curriculum (Box 1) and focus on clinically relevant dilemmas commonly faces when managing these patients.

Background & Clinical presentation

PSC is a chronic auto-immune liver disease characterized by progressive cholestasis, inflammation and fibrosis affecting both intra and extrahepatic bile ducts[1]. This leads to multiple biliary strictures which predisposes to infection, malignancy and progresses to cirrhosis and chronic liver failure. The pathogenesis of PSC is complex and multifactorial and a reflection of converging genetic and environmental risk which result in chronic fibrosing biliary injury from a combination of immune dysregulation, altered gut microbiota and abnormal bile homeostasis[2]. Commonly a combination of otherwise unexplained biochemical cholestasis for at least 6 months plus characteristic changes on Magnetic Resonance Cholangiopancreatography (MRCP) or liver biopsy is accepted as leading to a confident diagnosis of PSC[1]. Endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for therapeutic procedures and is not recommended for diagnosis, in keeping with substantial risks of cholangitis and pancreatitis. More detailed description of the clinical presentation can be found in Box 2.

Most patients with PSC have evidence of both intra and extrahepatic bile duct disease. Isolated large bile duct stricturing occurs in <5% of PSC patients, and should raise the possibility of an

alternative or additional diagnosis such as cholangiocarcinoma[1]. Fewer than 25% of patients experience isolated intra-hepatic disease, so called "small-duct PSC"[1], which may be diagnosed in the context of chronic cholestasis but normal MRCP, with a liver biopsy suggestive of PSC +/- co-morbid inflammatory bowel disease (IBD). Diagnostic criteria for small duct PSC should focus on the presence of characteristic disease defining histology; disease that remains restricted to small ducts only has a better prognosis[1].

In keeping with limited disease insights, overlapping and cross-over presentations are encountered, particularly in younger patients[3]. Further discussion of this is beyond the scope of this article. Similarly in all patients, IgG4 associated systemic disease should be considered and excluded, usually on the basis of IgG4 measurement and imaging review.

Management dilemmas

Current management relies on symptomatic control of itch, pain and cholangitis with close monitoring for complications. A majority of patients will become established on a path to relentless fibrosis and cirrhosis making timely referral for consideration of transplantation important, particularly given the unpredictable nature of obstructing biliary disease. Orthotopic liver transplantation usually for advanced parenchymal disease or recurrent cholangitis will result in an average of 80% 10 year survival[1]. PSC accounts for around 10% of liver transplants worldwide and is the 5th most common indication for transplantation in the UK[4]; although the rarest of the autoimmune liver diseases PSC is now the leading disease indication for transplantation within the family of autoimmune liver diseases. Despite this, recurrent PSC in the graft has been described in up to 30% within the first 5 years post transplantation[1]. Immunosuppressive agents have no role in PSC management unless there is strong evidence of overlap with AIH, which must include convincing liver histology.

Frequent management dilemmas faced by clinicians include:

1) **Ursodeoxycholic Acid**

Ursodeoxycholic acid (UDCA) is one of two drugs licenced for PBC, however it remains controversial in PSC. Large trials have failed to prove statistically significant improvement in fibrosis on liver biopsy or in symptoms, although biochemistry can be markedly improved with UDCA[1]. At higher doses of 28-30mg/kg/day, a large multi-centre study was terminated early, due to increased risks of liver transplantation and varices development in the UDCA-treated cohort (many of whom who already had late-stage cirrhosis)[1]. Due to these concerns, current guidance cannot make an evidence-based recommendation to use UDCA[1], and it is notable that transplantation rates for PSC have, unlike PBC, not changed over time despite liberal use of UDCA at times. Additionally no data supports a role for UDCA in cancer chemoprevention.

2) **Managing cholangitis and the role of ERCP**

Recurrent cholangitis is a common complication of PSC and can result in the need for repeated hospital admissions. Fever and raised inflammatory markers are not always seen however a sudden increase in the level of pruritus or worsening biochemistry that responds to antibiotics is key. Cholangitis can often be managed in the community, with intermittent short courses of appropriate oral antibiotics (e.g. ciprofloxacin) kept at home for patients to commence themselves however short courses of intravenous antibiotics may be required. Patients experiencing multiple episodes of cholangitis per year can respond well symptomatically to long term rotating low-dose prophylactic antibiotics, however long term benefit from this has not been proven. Patients with severe recurrent cholangitis can be considered for liver transplantation, independently of the severity of their liver dysfunction, as should all patients with advanced PSC[1].

Recurrent cholangitis is a feature of the natural history of PSC and biliary intervention needs much thought, as benefit and risk are finely balanced in PSC. ERCP may have a role in the therapeutic management of a dominant biliary stricture when clinically indicated: the dilemma is in definitions and whilst cholangiography can be used (strictures are considered dominant if there is a <1.5mm stenosis in the common bile duct (CBD) or <1mm in the right/left hepatic ducts[1]), in practice a better definition is the combination of clinical, laboratory and imaging findings, after appropriate MDT review. Development of a new biliary stricture requires exclusion of cholangiocarcinoma and potentially decompression of biliary obstruction. This may reduce ongoing liver damage as well as alleviate some symptoms of pruritus and recurrent cholangitis. However, not all strictures are responsible for symptoms and not all are amenable to endoscopic intervention. Endoscopic programmes include short-term stenting with plastic stents or repeated balloon dilatation attempts (the latter more commonly chosen), however the evidence for these is unclear[1].

3) Managing concomitant IBD and colonic neoplasia risk

PSC-IBD is a clinical entity subtly distinct from classical ulcerative colitis or Crohns disease[5] and is co-morbid in up to 75% of PSC[6]. Bowel symptoms can be mild or even completely absent; therefore recommendations are for a baseline colonoscopy (with segmental biopsies) in those not already known to have IBD, regardless of bowel symptomology[1]. A diagnosis of PSC-IBD has significant prognostic implications, with a 20-30% risk of colonic carcinoma over 20 years compared to a 5% risk of the same in ulcerative colitis without PSC[7]. Thus, in the presence of PSC-IBD, colonoscopy is generally repeated annually from the time of PSC diagnosis[1]. Dye-spray surveillance is likely appropriate, as may endomicroscopic techniques be in the future.

Colitis management in PSC-IBD resembles that of IBD alone. Overall good control of IBD activity (i.e. mucosal healing where possible) is important, although it is not clear if this impacts beyond

the colon into liver outcomes. Annual colonoscopic surveillance continues post-transplant, and attention is important to potentially clinically significant flares post-transplant, that may require prompt biologic therapy (e.g. Vedolizumab) or colectomy, frequently in the presence of pristine liver graft function. Recurrent disease appears associated with the presence of an intact colon post-transplant. In those patients contemplating pouch surgery, it is important to counsel for a higher rate of pouchitis in PSC-IBD subjects, and an association with recurrence for those with pouchitis post-transplant.

4) Hepatobiliary Malignancy risk in PSC

PSC patients are at significant risk of hepatobiliary malignancies most commonly cholangiocarcinoma (CCA), gallbladder adenocarcinoma and occasionally hepatocellular carcinoma (HCC). Patients with PSC have a CCA lifetime risk of 10-15%, a third of which are diagnosed within 12 months of the PSC diagnosis (albeit this is a risk clearly augmented with increasing age at diagnosis)[1]. Distinguishing CCA from PSC alone can be difficult, so a high index of suspicion must be held over any dominant stricture or other sudden worsening in biochemistry or imaging. It is currently not possible to predict which individuals are most at risk and this does not correlate well with severity of symptoms or parenchymal disease[1]. ERCP with brush cytology is traditionally used to investigate a possible cholangiocarcinoma or dominant large bile duct stricture, however this has a relatively low diagnostic yield and negative brushings do not provide absolute reassurance of the absence of cancer. Newer techniques have evolved to increase yield at ERCP which may improve diagnosis, for example Fluorescence In Situ Hybridization (FISH), Digital Image Analysis (DIA) or direct visualisation of the biliary tree via digital cholangioscopy (SpyGlass). CA19-9 can be raised in both PSC and CCA so is not frequently useful for diagnosis and overall routine surveillance for cholangiocarcinoma is cannot currently be recommended based on evidence of efficacy. A combination of non-invasive imaging, CA19-9 and ERCP with sampling

may provide better detection rates and investigation via these modalities should be considered whenever there is clinical concern about the development of cholangiocarcinoma[1].

Gallbladder cancer is diagnosed in 2% of PSC patients with half of gallbladder lesions proving to be adenocarcinoma[1]. Therefore, yearly ultrasound imaging is recommended for patients with PSC, and HPB consultation important with a view to cholecystectomy, if gallbladder polyps are identified[1]. 6 monthly ultrasound scanning should be commenced for HCC surveillance once cirrhosis is confirmed.

New Treatments, clinical trials and prognosis

PSC is an orphan disease with no current disease-modifying therapy nor any validated risk stratification tools[8]. Currently, the median time from diagnosis to liver transplantation or death is between 13-21 years[9] with significant healthcare resource use and symptomatic needs. PSC thus represents a high unmet need for patients, and those at particular risk of progression (usually identified by active biochemical cholestasis) are encouraged to enter clinical trials. Box 3 describes the currently recruiting interventional clinical trials as listed on clinicaltrials.gov, demonstrating an ongoing interest in disease modification tackling a broad spectrum of biologic targets.

Case Examples:-

Case 1) Mr A presented generally unwell aged 17 and was found to have an ALT >300U/L with normal ALP, bilirubin and liver synthetic function. ANA was weakly positive and IgG was 19.1g/L. Ultrasound was normal. Non-invasive liver screen was negative and there was no significant family or travel history. He underwent a percutaneous liver biopsy which showed significant fibrosis, with moderate portal inflammation and piecemeal necrosis. A diagnosis of auto-immune

hepatitis was made and prednisolone 30mg was commenced. After four weeks there was no improvement so he was referred to tertiary hepatology services.

On further review, Mr A was found to also have a raised GGT at 641U/L. MRCP confirmed prominence of the intra-hepatic biliary tree with evidence of short strictures, consistent with PSC. He had also been suffering from some mild diarrhoea but this had resolved since starting the prednisolone. He underwent colonoscopy confirming active ulcerative pan-colitis and commenced mesalazine followed by azathioprine, gaining good colitis control off corticosteroids. Liver tests improved markedly after this with ALT 104U/L and GGT 258U/L.

This case demonstrates an inflammatory sub-group of PSC, especially as a presentation in adolescents initially treated as AIH. It can be difficult to distinguish between AIH and inflammatory PSC however a high index of suspicion is relevant, especially in young men with a history of bowel symptoms. In young patients GGT has better sensitivity for biliary disease than ALP; additionally in the newly presenting patient with early PSC-IBD, it is not infrequent to observe an improvement in liver biochemistry with effective IBD management.

Case 2) Mrs B was a healthy 49 year old woman who underwent a routine laparoscopic cholecystectomy for cholelithiasis. At the time of surgery it was noted that her liver looked abnormal and a biopsy was taken. Liver histology showed non-specific abnormalities including reactive changes and mild fibrous expansion of the portal tracts. She became lost to follow up but presented 7 years later with profound painless jaundice and weight loss. Non-invasive liver screen was negative. An ultrasound showed evidence of cirrhosis with splenomegaly. ERCP showed a narrow irregular CBD and a diagnosis of PSC was made. UDCA was commenced followed by referral to tertiary hepatology services.

Upon review she remained jaundiced with a bilirubin of 160µmol/L and UKELD of 54 (MELD 31). She described worsening itch, fatigue and steatorrhea. UDCA was stopped and hydralazine as well as cholestyramine commenced, with resulting improvement in itch and bowel symptoms. While awaiting an MRCP, she deteriorated with a bilirubin of 400µmol/L and UKELD 60 (MELD 35), so she was admitted for liver transplant assessment. MRCP confirmed dilated intrahepatic bile ducts with beading abnormalities and suggested a hilar stricture. Despite clinical concern over the possibility of CCA, no objective evidence of this could be found on imaging. Given her rapid clinical deterioration she was accepted onto the liver transplant list and she received a whole liver graft 5 days later.

Explant histology confirmed a T4 N1 poorly differentiated cholangiocarcinoma with lymph node spread and possible involvement of the distal bile duct margin. Mrs A received best supportive care and died soon after this.

This case highlights the need to maintain follow up on patients with possible early liver disease to ensure accurate diagnosis and timely referral for further management or transplantation. Diagnosis of CCA can be elusive and it remains that transplantation may be considered and offered, despite accepted uncertainty, with cancer identified only on explant evaluation.

Case 3) Mr C presented aged 16 with diarrhoea and abdominal pain. Flexible sigmoidoscopy was normal however colonoscopy confirmed moderately active right-sided colitis and mesalazine was commenced. Multiple courses of corticosteroids were required to gain colitis control, followed by the introduction of azathioprine. It was noted that Mr C had deranged LFTs, with ALP 474U/L and ALT 195U/L. MRCP showed beading within the intrahepatic bile ducts and a diagnosis of PSC-IBD was made followed by a referral to tertiary hepatology services.

This was followed by multiple admissions to hospital feeling generally unwell, feverish and with a transiently raised bilirubin. Inflammatory markers were normal however symptoms swiftly resolved after the introduction of antibiotics for presumed recurrent cholangitis and pausing of the azathioprine. In between these episodes Mr C remained well and was planned for active surveillance, with yearly ultrasound and colonoscopy. However, the episodes of cholangitis persisted so he commenced a rotating pattern of sequential prophylactic antibiotics and azathioprine was stopped. Plans were made for a 10 day course of IV antibiotics in the community if oral antibiotics did not settle things down and for further bowel investigations to ensure that his IBD was completely under control.

This case demonstrates that cholangitis can be difficult to manage and may result in repeated admissions to local and specialist services. Often symptoms are subtle and patients do not necessarily present with typical signs of infection yet can deteriorate very quickly without appropriate treatment. A low threshold should exist for trialling a course of ciprofloxacin in these patients as well as looking for driving factors such as active IBD or a dominant stricture.

A selection of best of 5 questions can be seen in Box 4 with answers in Box 5.

Competing Interest: No relevant disclosures.

Box 1. Gastroenterology 2010 curriculum competencies

2) Core Competencies e) Hepatology Specific diseases	Auto-immune liver disease including auto-immune hepatitis, PBC, PSC and overlap syndromes:- - Awareness of management and complications of autoimmune liver disease including the malignant complications in PSC. - Appreciate and understand that this range of liver disease is frequently under diagnosed and may have been inappropriately managed.
3)Advanced Specialist areas a) Hepatology	Complications of Cholestatic Liver Disease:- - To be able to carry out specialist assessment, investigate, diagnose, initiate treatment of patients with cholestatic liver disease (e.g. PBC, PSC) and exclude large duct obstruction. - Able to assess individual patients concerning the timing of potential transplantation. - Selects and uses investigations appropriately (specifically in PSC,) to be aware of possible inflammatory bowel disease and regimes for colonoscopic surveillance.

*Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC)

Box 2. Epidemiology and clinical features of Primary Sclerosing Cholangitis (PSC)

Epidemiology	Prevalence of up to 16.2 per 100,000 inhabitants[10]. 60% of sufferers are male[1]. Mean age 30-40 years[11].
Associations	Non-smokers[1]. Inflammatory bowel disease is seen in up to 80%[1].
Symptoms	Pruritus, right upper quadrant pain, fatigue, fevers/chills, recurrent cholangitis. Severity of symptoms does not correlate well with the severity of liver dysfunction, biochemistry or imaging or the malignant risk[1].
Diagnosis - Biochemistry	50% of patients are diagnosed at the early, asymptomatic stage[1]. Cholestasis (i.e. raised ALP, GGT and/or bilirubin). Liver synthetic dysfunction if advanced parenchymal disease. ALT/AST often mildly raised in the range of 2-3 times normal[1].
- Serology	Non-specific and not required for a diagnosis. Immunoglobulin G can be up to 1.5 times normal in 60% of patients[1] but it is vital to check IgG subclasses to exclude IgG4 disease.
- Imaging	MRCP - usually the first line diagnostic test, aims to identify bile duct stricturing. Useful if diagnostic uncertainty or normal MRCP.
- Liver biopsy	Classical changes of periductal concentric fibrosis (“onion-skinning).
Differential Diagnosis	Secondary sclerosing cholangitis. IgG4 cholangiopathy. Ischaemic cholangitis. Inherited cholestatic diseases (e.g. ABCB4 deficiency).

*Alkaline Phosphatase (ALP), Gamma-glutamyl transpeptidase (GGT), Alanine transaminase (ALT), Aspartate transaminase (AST)

Box 3. Current interventional clinical trials in PSC

Full name	Sponsor	Location	Status
A Single-arm, Phase IIa, Safety and Efficacy Trial of Selected MSCs in the Treatment of Patients With PSC & AIH (Merlin)	University of Birmingham	UK	Not yet open
A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for 12 Weeks in Patients With Primary Sclerosing Cholangitis	NGM Biopharmaceuticals, Inc	USA & Europe	Open to recruitment
Fecal Microbiota Transplantation for the Treatment of Primary Sclerosing Cholangitis.	Brigham and Women's Hospital	USA	Open to recruitment
Safety, Tolerability, and Efficacy of GS-9674 in Adults With Primary Sclerosing Cholangitis Without Cirrhosis (PSC-Phase 2)	Gilead Sciences	USA & Europe	Open to recruitment
The Human Gastrointestinal Tract Microbiota in the Setting of Treating Primary Sclerosing Cholangitis and Biliary Atresia With Vancomycin	Sacramento Pediatric Gastroenterology	USA	Open to recruitment
A Single Arm, Two-stage, Multi-centre, Phase II Clinical Trial Investigating the Safety and Activity of the Use of BTT1023 Targeting Vascular Adhesion Protein (VAP-1), in the Treatment of Patients With Primary Sclerosing Cholangitis (PSC).	University of Birmingham	UK	Open to recruitment
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding, Clinical Trial Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects With Primary Sclerosing Cholangitis	Intercept Pharmaceuticals	USA & Europe	Ongoing, Closed to recruitment
Treatment of Primary Sclerosing Cholangitis in Inflammatory Bowel Disease Patients With Oral Vancomycin by the Study of Its Antimicrobial and Immunomodulating Effects	Stanford University, USA	USA	Ongoing, Closed to recruitment
A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of GS-6624, a Monoclonal Antibody Against Lysyl Oxidase Like 2 (LOXL2) in Subjects With Primary Sclerosing Cholangitis (PSC)	Gillead Sciences	USA & Europe	Closed, Awaiting results

Box 4. Best of 5 Questions for the gastroenterology SCE

1)	Ms D is a 35 year old lady who has undergone a liver biopsy. **Which histological features would be most in keeping with a diagnosis of PSC?** a) Focal duct obliteration with granuloma formation b) Hepatocyte ballooning, Mallory-Denk bodies and lobular inflammation c) Interface hepatitis with resetting and central portal bridging necrosis d) Periductal concentric fibrosis e) Piecemeal necrosis with periportal inflammation
2)	Mr E is a 45 year old man with a 25 year history of PSC. He has a history of recurrent cholangitis not controlled with daily rotating antibiotics and worsening pruritus despite daily cetirizine and cholestyramine sachets thrice daily. His investigations are as follows:- Hb 101g/L WCC 3.1x10*9/L Platelets 100x10*9/L INR 1.4 Sodium 131mmol/L Urea 3.1mmol/L Creatinine 43µmol/L Alb 32g/L ALT 23U/L AST 20U/L Bilirubin 67µmol/L ALP 587U/L Ultrasound – course liver parenchyma with irregular edge, splenomegaly, no ascites MRCP – multi-focal biliary stricturing with peripheral dilatation **Which of the below options is the likely optimal management plan for him?** a) Admit to hospital for a 7 day course of IV Merepenem b) Commence rifampicin c) Commence UDCA d) ERCP with balloon dilatation and/or plastic stent insertion e) Refer for liver transplant assessment
3)	Mr F is an 18 year old man who presents with a 2 month history of abdominal pain and diarrhoea up to 3 times per day with occasional streaks of blood. Investigations are as

	follows:- Hb 135g/L WCC 5.1x10*9/L Platelets 361x10*9/L INR 0.9 Sodium 139mmol/L Urea 4.1mmol/L Creatinine 63µmol/L Alb 37g/L ALT 55U/L AST 60 U/L Bilirubin 23µmol/L ALP 295U/L Colonoscopy – moderately severe pancollitis. 5ASA commenced. MRCP – slight beading of the intrahepatic bile ducts **What would be the next best management strategy for this patient?** a) Commence Azathioprine b) Commence UDCA c) ERCP d) Liver biopsy e) Repeat biochemistry in 4-6 weeks

Box 5. Best of 5 Questions for the gastroenterology SCE – Answers

1)	Focal duct obliteration with granuloma formation is associated with PBC. Hepatocyte ballooning, Mallory-Denk bodies and lobular inflammation are features of NASH. Interface hepatitis with resetting and central portal bridging necrosis are associated with AIH. Piecemeal necrosis with periportal inflammation is associated with PSC-AIH overlap. Periductal concentric fibrosis is highly suggestive of PSC therefore d) is the correct answer.
2)	Admission for a course of IV antibiotics can help provide relief but this is short term and he has significant liver synthetic dysfunction so more definitive management is required. While rifampicin is next to try for intractable pruritus according to guidelines, caution is required with this level of synthetic liver dysfunction and would again only be a holding measure. UDCA is not currently recommended in PSC and can worsen pruritus. There is no dominant stricture or signs of biliary obstruction so ERCP would not be recommended in this situation and would have risk risks of precipitating worsening cholangitis. Mr E has a Child-Pugh score of 8 giving Class B disease, plus has an indication for transplant (intractable cholangitis) and a UKELD score of 58 (MELD 20). Therefore e) is correct in this instance.
3)	In a young man with IBD and deranged LFTs which are of a cholestatic nature, PSC is top of the differential diagnosis list. While transaminases and IgG are slightly raised, this is non-specific and insufficient evidence of possible PSC-AIH overlap to justify liver biopsy at this point or commencement of further immunosuppression. UDCA is not currently recommended in PSC and there is no indication for ERCP. Liver biochemistry may improve significantly with IBD control. a) Is the correct answer.

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